

(Interview of February 10th, 2005)

ActivX Biosciences

Private Equity

Dr. John Kozarich, PhD

Chairman, President and Chief Scientific Advisor of Kyorin
Pharmaceutical Company

ActivX Biosciences is pioneering the field of activity-based proteomics to increase the speed and cost-effectiveness of target discovery and drug development. The company is developing a high-throughput chemistry platform for identifying and analyzing active proteins in all ranges of abundance in any biological sample. Using this technology, ActivX is solving the most important problems in drug discovery and development: the identification of novel drug targets, the determination of target selectivity for drug candidates, and the assessment of efficacy and toxicity for candidate and established drugs.

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Dr. John Kozarich, Chairman, President and Chief Scientific Advisor of Kyorin, spoke with *Wall Street Reporter Magazine* on February 10th, 2005.

WSR: For those who haven't followed ActivX Biosciences, let's start with an overview and recap of the 2004 year.

KOZARICH: The company was founded in late 2000 to set up a new type of protein-based analysis technology that allows us to look at large families of proteins that are pharmaceutically of interest to people in drug discovery and to address issues of drug selectivity and toxicity. 2004 turned out to be a very challenging year for us. We

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began the year with very high hopes for our own internal drug discovery program in the area of neutropenia, looking for an oral drug to treat chemotherapy-induced neutropenia. Midway through the year, we ran into inevitable issues with idiosyncratic toxicities in certain animal species, which put a damper on the financing that was proceeding at that time. Given the sentiments in the market for companies that are fairly far along in development, we made a strategic shift and approached one of our key collaborators, Kyorin, who had expressed an interest in setting up a significant U.S. presence, to explore the possibility of acquiring the company. Needless to say, we were successful in that endeavor.

WSR: Taking a look at the company's technology vis-a-vis other technologies out there, what is giving you the key competitive advantage in this space?

KOZARICH: I think it is the ability to use our technology in real tissues, across species, to get at the most difficult drug discovery issue, which is drug selectivity. As you may know, many drugs fall out in clinical development because of unanticipated toxicities, and quite often these are due to interactions with proteins related

to the actual drug target. As an example, our collaboration with Pfizer, which has recently been expanded, was initially focused precisely on that issue. As a matter of fact, our initial collaboration with Pfizer was not, interestingly enough, with the early drug discovery team; it was actually with the safety assessment team.

WSR: What trends in big pharma affect the way in which you market to the needs of others in the drug discovery efforts, and how do they shape the company's mission?

KOZARICH: I think that the ability to save big pharma money downstream in terms of development is really part of the game now in the industry. The costs of preclinical and clinical development are increasing exponentially and the sooner one can address those issues upfront, the better off the company will be. For example, in the Pfizer collaboration, the sentiment in the safety assessment group was that if they had had this information a couple of years earlier, they might have made different decisions in terms of how they would have proceeded with their programs.

WSR: Tell us a bit more about the integrated chemical tools and the infrastructure developed around it.

KOZARICH: We have focused on developing tools that allow us to interrogate very large pharmaceutically-interesting protein families. The ones that we are specifically focusing on now, internally, and also with our collaborators are in the areas of kinases and proteases. Those two protein families, right now, are the subject of lot of action in the pharmaceutical and biotech drug discovery scene and especially in the area of kinases, where issues of drug selectivity are really problematic. As an example, there are probably 400 or 500 different protein kinases and, for most of them, no useful assays are developed and quite often even the biology is not well understood. Our technology allows one, in an unbiased way, to analyze different tissues to see if their drug is as selective as they think it is, or if it does hit other kinases for which they may not currently have any assays. This can be extremely valuable for deconvoluting issues of toxicity.

WSR: What are some of the other growth opportunities that you are addressing with these markets?

KOZARICH: As an example, our initial collaboration with Kyorin was to design a selective drug that would be useful in Type 2 Diabetes which of course is, potentially, an absolutely huge market. Kyorin has focused in recent years on metabolic diseases and respiratory diseases in general. In the area of diabetes and obesity, they have had compounds in clinical development with Merck in the area of the PPAR compounds, another hot area in drug discovery, and also in respiratory diseases, looking for drugs for COPD, Asthma and so on.

WSR: In terms of the Kyorin acquisition, what can we expect as a result of the recent closing?

KOZARICH: Kyorin is a very interesting mid-size Japanese company. They have a fairly small number of employees, only 350 in R&D. On the other hand, they make money; this past year they probably had on the order of about \$750 million in sales and they show black ink. They were very impressed with our technology and its ability to get them to a clinical candidate; we anticipate filing an IND later this year in our Type 2 Diabetes program. For Kyorin, this was actually the fastest development program from initiation and conception to a preclinical development candidate that

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they've ever had. And I think for a smaller company like Kyorin in Japan, where they are facing competition from many of the bigger players in Japan, this type of competitive advantage was viewed by them and their President, Mr. Ogihara, as being critical for their future success.

WSR: What are the other intangibles that are going to give you a competitive advantage in this market space?

KOZARICH: Kyorin has excellent strength in the more traditional pharmaceutical areas of drug discovery like medicinal chemistry and pharmacology, and we provide them with that technological edge. One of the intangibles here is that Kyorin has looked favorably on us maintaining our collaboration business. Indeed, I stressed to them during the negotiations that the use of ActivX as a means for them to network in the U.S. pharmaceutical and biotech scene was a real advantage for them because we could collaborate with other companies like Pfizer on topics where we were not in direct competition with them. That would allow us to first, continue to develop and strengthen our technology, which Kyorin would benefit from, and also to start building our

own database of information just by virtue of the type of work we are doing with other companies.

For example, Kyorin currently has a quinolone antibiotic marketed with Bristol Myers Squibb. In the past, they have had a quinolone norfloxacin, the very first quinolone antibiotic, which they marketed with Merck. So, their entry into the U.S. market is dependent upon the types of relationships they can set up with the U.S. pharmaceutical industry. So, the Pfizer collaboration is a natural, and in reality, Pfizer viewed our acquisition quite favorably because they realized that this provided us with the stability element that assured them that they could approach us about a longer-term collaboration.

WSR: How will you capitalize on this new improved drug discovery network that you highlighted in the announcement of the acquisition?

KOZARICH: We are Kyorin's very first entree into the U.S. research market and San Diego was an ideal site for them. They also have a research operation through the Scottish Biomedical Research Counsel in Glasgow and a joint venture with Nisshin Pharmaceutical called Nisshin Kyorin. So, they

viewed this presence in the U.S. as a critical component to establishing a network which allows them to parlay their own internal capabilities. Although the initial ActivX site here is focusing on basic research, the goal is for Kyorin to begin expanding its presence in preclinical and clinical development in the U.S. and to use ActivX as their base of operations for that.

WSR: What are the multiple discovery and development stage products that we could expect to see going into effect?

KOZARICH: As I mentioned, our technology sweet spot is in the area of proteases and kinases. And so, we are currently using our technology in collaboration with Kyorin for programs in those two target areas that fit well with their own therapeutic interests, i.e., metabolic diseases, respiratory diseases and immunology. And so, our initial programs will focus on those particular aspects. In addition, our technology has been very useful for profiling compounds that are already entering into clinical development. As a result, we are taking responsibility for profiling Kyorin compounds that are in clinical development. They currently have compounds in Phase IIb clinical trials for dyslipidemia, a PPAR compound, and a

compound, an immunomodulator, that is also in clinical trials. So, they were very astute early out in seeing the value of our technology, both early in discovery and also later on in clinical development.

WSR: In terms of the integration of the acquisition on their side as well as the synergies gained, how quickly will this be done and will the synergies continue through the course of this year?

KOZARICH: We have gotten out of the box pretty quickly in that regard. We had a major joint meeting here in San Diego just a little over a week ago where scientists from both ActivX and Kyorin spent two days working on integrating the research program, from the standpoint of our technology and their capabilities and strengths and medicinal chemistry and pharmacology. So, the teams have, over the past two-and-a-half years through the collaboration, established a fair amount of rapport. Also, I have had a long-term relationship with Kyorin over 13 or 14 years from my days at Merck. And so, I think one of the key issues in terms of these sorts of acquisitions is having the kind of personal rapport with the other groups to really cut through the red tape.

WSR: In your press announcement you refer to 'a new paradigm' here in a U.S.-based Japanese research center. How much of this is a new paradigm, and what are the dynamics of it?

KOZARICH: There have been many Japanese companies that have set up research institutes in the U.S., and with maybe one or two exceptions, they tend to try to build up a research institute as a stand-alone entity. For example, Chugai Research Institute that was here in San Diego has closed down recently. Sankyo, Takeda, Esai and a number of other companies have gone down this road.

The paradigm we wanted to stress here was, rather than try to build up an insulated research institute, to leverage the strengths of a biotech company and its ability to be networked into the environment. At Activx, we have excellent networking and accessibility to Scripps. As a matter of fact, our original technology came out of Scripps. Kyorin has been very careful to continue to cultivate those relationships with Scripps and with the San Diego community, and they will be able to do that through me and through ActivX. So, I think that for this sort of a

Japanese research institute endeavor, having that kind of dynamic to get those interactions will only synergize the ability to get things done. One of the issues with many of the other research institutes coming to the U.S. is that they try to build them as an insulated stand-alone entity and quite often they just don't mesh culturally with the U.S. scene.

WSR: With regard to the strategic collaboration and agreement with Pfizer, how will the underlying strategy or the dynamics change there?

KOZARICH: Initially, our first collaboration with Pfizer focused on a beta test with safety assessment and the safety assessment group saw the value of the technology in some ways much more rapidly than the early drug discovery people. What we are doing now with Pfizer is expanding the collaboration, which began in La Jolla, to involve every site at Pfizer (with the exception of the site in Sandwich, England), spanning about half a dozen different projects -- not only the safety group, but also now early drug discovery. So, it's an opportunity for us to demonstrate the breadth of the technology and it's an opportunity for

Pfizer to "kick the tires" to see what the scope of the value is for them.

WSR: Based on your vision, how you would characterize the next two to three years for ActivX, going ahead?

KOZARICH: Kyorin is onboard with respect to our business strategy, and that acquisition gives us stability. What we hope to do is to be very successful in providing Kyorin with preclinical candidates for further development and to serve as a base of operations for them that can be expanded into preclinical and clinical development. Also, we hope to provide them with the networking that is very important in terms of building their U.S. business, and reach the goal not only of providing Kyorin with entrees to companies like Pfizer, but also vice versa. I think Pfizer is quite intrigued by the Kyorin collaboration because big companies like Pfizer are mindful of the fact that the Japanese companies are a potential source of new pipeline drugs, so these interactions may blossom into deeper business interactions.

WSR: Looking at this deal as a whole, how do you feel it will affect trends for Asian biotech companies as well as partnering trends as a whole?

KOZARICH: I was rather surprised by an announcement a couple of days ago that Syrrx, a biotech company here in San Diego, was just acquired by Takeda. The model they are using is exactly the one we have established with Kyorin, in that Takeda is allowing Syrrx to continue its collaboration business but has acquired them to provide a technology that they feel they need. So, I was pretty gratified to see that. It may be a coincidence, but at least it looks like someone else is going down the same road with that kind of a model.

WSR: In terms of milestones, what should we expect to see in 2005 from ActivX?

KOZARICH: I am committed to building our collaboration business, as well as the Kyorin drug discovery business. I think the two of them give us a potentially interesting growth profile, and down the road there may be opportunities to ultimately spin parts of ActivX out into the public markets again. Or Kyorin may be so happy with

the way things are going and they may find this model to be one that works. So, the challenge for us here at ActivX in the next couple of years is to demonstrate to Kyorin and to the community at large that this is an interesting model that may ultimately be another path to success for biotech companies that have hit rather rocky roads, especially those that started out as technology platform companies.

WSR: Final words here, what is the most compelling reason for people to continue to follow ActivX?

KOZARICH: The ActivX technology really works. Kyorin is convinced with it, and we have provided Pfizer with data to show that it works, and they are now attempting to see how convinced they are. So, it's a technology that we spent a lot of time making very valuable for drug discovery and development. And I think the next couple of years will give us the real data points to show that the technology works.

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